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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/56, 31/705

A1

(11) International Publication Number: **WO 99/52532**

(43) International Publication Date: 21 October 1999 (21.10.99)

(21) International Application Number: PCT/US99/07319

(22) International Filing Date: 2 April 1999 (02.04.99)

(30) Priority Data:
09/059,184 14 April 1998 (14.04.98) US

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(81) Designated States: AU, CA, JP, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: METHOD FOR REDUCING CENTRAL NERVOUS SYSTEM IMPAIRMENT

(57) Abstract

The present invention is related to a method for reducing central nervous system (CNS) impairment, such as results from an ischemic event caused by a stroke or trauma to the central nervous system. In accordance with the present invention, CNS impairment is reduced by administering a dehydroepiandrosterone (DHEA) congener as soon as possible after the ischemic event.

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METHOD FOR REDUCING CENTRAL NERVOUS SYSTEM IMPAIRMENT

BACKGROUND OF THE INVENTION

The present invention is related to a method for reducing central nervous system (CNS) impairment, such as results from an ischemic event caused by a stroke or trauma to the central nervous system. In accordance with the present invention, CNS impairment is reduced by administering a dehydroepiandrosterone (DHEA) congener as soon as possible after the ischemic event.

The publications and other materials used herein to illuminate the background of the invention, and in particular cases, to provide additional details respecting the practice, are incorporated by reference, and for convenience are numerically referenced in the following text and respectively grouped in the appended bibliography.

Every year, nearly 500,000 people in the United States suffer a stroke. Although most of them survive, approximately 67% develop disabilities related to the stroke. It is estimated that there are over two million stroke survivors in the U.S. who are handicapped from paralysis, loss of speech and loss of memory. These individuals impose enormous costs to society, both in health-care dollars and in loss of productivity. Despite some improvements in health care treatment of strike victims, this condition ranks third behind heart disease and cancer as a cause of death among Americans.

A stroke is a severe, localized brain tissue injury resulting from a sudden decrease in blood flow. Because it has no capacity of storing oxygen or glucose at effective concentrations, the brain requires a constant blood supply. A lack of blood flow to the brain for just 8-10 seconds can lead to dysfunction, most of which is reversible. Insufficient blood flow for more than five minutes will cause irreversible brain damage.

Clinically, the first and most frequent cause of stroke is a blocking of one of the four major blood vessels that carry blood to the brain, causing focal ischemia and necrosis of brain tissue. These vessels converge at the base of the brain and give off numerous branches which represent a secondary source of blood supply to the brain. The amount of damage created by blockage of blood vessels is therefore dependent on the total amount of blood vasculature in a section of brain. Blockage of a blood vessel will cause significant damage if there is no alternative source of blood supply, while blockage of another branch may actually go unnoticed by the individual if there is a supplementary supply. Focal ischemia of the brain manifests itself

clinically in three stages in humans. The first is transient ischemic attacks, which are followed by rapid recovery. The second is stroke-in-evolution, where irreversible injury is progressing under observation. The third is the completed infarction. Surrounding the core of ischemic tissue (the area directly devoid of blood flow) is the ischemic penumbra. This second area, reduced of blood supply by only 20-50%, is at risk for cell death due to vascular reperfusion injury and direct neurotoxicity induced by extreme fluctuations in intracellular calcium.

Researchers believe there are many mechanisms at work causing brain damage from stroke. The series of biochemical processes leading to cell death, known as the ischemic cascade, usually begins as blood flow is cut off with the loss of the ability of the cells to produce energy, particularly adenosine triphosphate (ATP). While brain cell death and injury occur rapidly within the core area following the attack, it takes place more slowly in the penumbra.

The microvasculature undergoes vigorous reaction to ischemia. Endothelial swelling occurs and luminal diameter decreases within minutes; after recanalization, one can see a brief reactive hyperemia in the ischemic tissue followed by chronic insufficiency of blood flow. This seems to be due to a change in microvascular tone. The blood brain barrier also appears to be disrupted in the ischemic territory and the coagulatory signal "tissue factor" is exposed (by the disruption of vascular endothelial cell tight junctions), apparently causing widespread fibrin deposition at sites remote from the blockage. Leukocytes and platelets stream to the ischemic territory, sometimes occluding the microvasculature. There is also rapid endothelial cell surface expression of selectins and intercellular adhesion molecules (which are involved in transposition of leukocytes from the blood stream to the brain).

There are also inflammatory components to the tissue response to ischemia. Mice made neutropenic are known to suffer smaller infarcts than normal mice. Anti-neutrophil trafficking agents are thought to be able to reduce infarct size.

In neurons, the maintenance of large ionic gradients across cell membranes is a principal consumer of energy and is dependent on the oxidative production of ATP. These gradients set up electrical potential differences across neuronal cell membranes that allow electrical signaling and neurotransmitter release. Maintaining ion concentrations, both intracellularly and extracellularly, is crucial for normal brain function. ATP-dependent, ion-specific pumps move their ions up concentration gradients (sodium ions out of cells, potassium ions into cells, calcium ions out), mostly across the plasma membrane, but also across the membranes of internal

compartments This means that a certain irreducible demand for oxygen, glucose and other nutrients exists in order to maintain an adequate supply of ATP ready for use by the cell.

Ischemia causes neuronal membrane depolarization (the inside of the membrane becomes more positive), acidosis (lactate accumulation from anaerobic glycolysis), and cessation of protein synthesis (not matched by a diminution in protein degradation). Depolarization causes an increase in intracellular calcium and an increase in extracellular glutamate. Calcium is a well-known intracellular second messenger whose internal concentration is tightly controlled and even localized. Sustained calcium concentrations above 300 nM are quite toxic. Uncontrolled increases of intracellular calcium activates proteases, kinases and phospholipases, produces free radicals while at the same time degrading a cell's ability to defend against them, further increases the release of calcium by opening calcium-gated conductances (releasing calcium from both internal stores and the extracellular space), and increases neurotransmitter release.

Ischemia causes the expression of immediate early genes in many cell types. The glia, which make up the largest fraction of the cellular volume of the brain, are intimately involved in the structure of synapses, and whose endfeet are closely apposed to the microvasculature, are also injured by ischemia. This limits control of the concentration of extracellular K^+ (which tends to cause neuronal depolarization) and glutamate. Many other glially dependent homeostatic mechanisms are also likely to be involved.

Just how vulnerable a nerve cell is depends on the extent of the cell's calcium overload and its ability to generate ATP as the energy source needed to kick out the excessive calcium ions.

One of the key findings in the past decade is that cells at risk do not necessarily die quickly, even though they may lose their ability to function. The total brain damage from a stroke can take hours or even days to reach its maximum effect. Intervention at different points in the cascade, therefore, could result in effective treatment.

Researchers are looking not only at clot-busting drugs like TPA and urokinase, which are thrombolytics, as well as clot-busting drugs with other mechanisms of action, but also at neuroprotectants. The former use a variety of mechanisms to break up the clot and normalize blood flow, presumably preventing an ischemic cascade or greatly reducing its impact. The latter interfere at various points in the cascade to prevent or reduce further damage to neurons.

Among the most widely researched neuroprotectants are glutamate antagonists, which block the rush of calcium into cells following a stroke; calcium channel blockers, which work to stop the intracellular buildup of calcium through electrically charged mechanisms; and calpain inhibitors. These prevent the release of the protease calpain which, when activated by the rush of calcium, breaks down other proteins. Another approach is kinase inhibitors, which prevent the release of various kinases, which block enzymes needed for ATP production.

Recent experiments suggest that the glutamate cascade is the major cause of neuronal death in hypoxia/ischemia (1-2). The exact underlying mechanisms of glutamate neurotoxicity are not yet well defined, but evidence suggests that glutamate triggers two distinct types of injury (3). The first is a reversible, acute neuronal swelling which depends on the influx of extracellular Na^+, Cl^- and water. The removal of either Na^+ or Cl^- from the media during an experiment eliminates the swelling (4). However, the absence of swelling does not ultimately protect the cells, since the neurons still die a few hours after being overexposed to glutamate. This delayed neuronal death is the second type of injury. It is dependent on extracellular Ca^{++} and is irreversible. Removal of extracellular calcium reduces excitotoxic injury in cortical cultures (5).

The rise in intracellular calcium concentration is believed to be necessary for both NMDA receptor-mediated normal functions (6) as well as NMDA receptor-mediated neurotoxicity. Calcium can activate a number of enzymes, including protein kinase C, cal modulin-dependent protein kinase II, proteases, and nitric oxide synthase (6-7). In addition to its ability to activate cytosolic enzymes, calcium can also activate endonucleases which may be involved in apoptosis (8). Excessive activation of any number of those enzymes mentioned can result in self-destruction. A hypothetical model of how glutamate can trigger transient injury and damage to neurons has been described (9-10).

Free radicals, formed during ischemic and post-ischemic periods, are thought to overwhelm endogenous protection mechanisms. These radicals are a group of highly reactive chemical species that can do extensive damage to lipids and proteins. Their actual importance in stroke has also been demonstrated by pharmacological interventions showing neuronal rescue.

There is evidence that nitric oxide (NO) might be a mediator of glutamate neurotoxicity (11). NO has been shown to mediate glutamate stimulation of cGMP accumulation, a process which is calcium-dependent and which is reduced in the presence of hemoglobin (Hb), a

scavenger of NO (11). NO can also react with superoxide anion ($O2^-$) to form perioxynitrite ($ONOO^-$) which can be toxic to neurons (12).

Knowledge about the role of glutamate in cell death during and after hypoxia-ischemia has opened many therapeutic possibilities. If each step in the cascade (9-10) could be blocked effectively, this would decrease the spread of neuronal damage and reduce the number of disabilities caused by stroke. One promising approach is to prevent the release of glutamate. This is theoretically possible with the use of adenosine agonists, drugs that stimulate the receptors of the chemical adenosine, which inhibits the release of neurotransmitters (13). Currently, available drugs of this type have cardiovascular and renal side effects (13). Another strategy is to lower brain temperature (9) in order to decrease brain activity and to conserve energy.

The easiest way to decrease neuronal damage caused by strokes is to directly interfere with the glutamate cascade. Most of the neurons exposed to excess glutamate or NMDA, even without swelling, eventually die (5). The fact that an influx of calcium accompanies hypoxic-ischemic injury (14) suggests that blocking this influx or the intracellular accumulation of calcium would be beneficial in treating stroke. Researchers have pursued the idea of both preventing glutamate activation and blocking the influx of calcium ions into the cell by using NMDA antagonists (drugs that prevent glutamate and NMDA from activating the NMDA receptors).

Available evidence suggests that antagonists of the NMDA receptor can provide significant protection against neuronal death caused by glutamate in tissue cultures and in animal models of stroke (15-16). There are several non-competitive NMDA antagonists whose neural protective efficacy have been well characterized and have been administered to humans. Data from clinical trials with the anticonvulsant MK-801 and the anesthetic ketamine have revealed unwanted side effects. Both of these drugs interact with the phencyclidine site on the NMDA receptor and are associated with schizophrenia-like symptoms similar to that produced by phencyclidine itself (17). Their clinical use is therefore limited. Two other NMDA antagonists are currently being tested for safety in humans: CGS 19755 and the cough suppressant dextrorphan (9).

There are other sources of calcium influx and accumulation such as voltage-gated calcium channels and release of calcium from intracellular storage. Calcium channel blockers

such as nimodipine, widely used in controlling hypertension and cardiac disease, are also being tried in stroke patients (17). Recently, three cell-permeant Ca^{++} chelators (BAPTA, 5,5'-difluoro BAPTA, and 4,4'-difluoro BAPTA) have been discovered and proven successful in treating neuronal ischemic injury *in vivo* (18). These chelators can easily penetrate the cell membrane and bind quickly to calcium inside the cell and therefore prevent intracellular calcium accumulation. They are a potential therapeutic strategy for the future treatment of stroke.

There are other possible approaches to inhibiting the post-synaptic events caused by glutamate activation. Antagonists at the other two types of glutamate receptor (quisqualate/AMPA and kainate) might also be useful in blocking the deadly effects of excess glutamate. The discovery of methods which reduce the psychomimetic effects of AMPA antagonists brings researchers a step closer to producing an effective drug with less dangerous side effects (19). There are drugs called free radical scavengers, such as 21-aminosteroid, which have shown some promise in reducing the infarct size in animal models of stroke, and are currently being tested in humans (17, 20).

Dehydroepiandrosterone (DHEA), a weak androgen, serves as the primary precursor in the biosynthesis of both androgens and estrogens (21). DHEA has been reported to play a mitigating role in obesity, diabetes, carcinogenesis, autoimmunity, neurological loss of memory (22-25), and the negative effects of GCS on IL-2 production by murine T cells (26). Araneo et al. (27) has shown that the administration of DHEA to burned mice within one hour after injury resulted in the preservation of normal immunologic competence, including the normal capacity to produce T-cell-derived lymphokines, the generation of cellular immune responses and the ability to resist an induced infection. Eich et al. (28-29) describes the use of DHEA to reduce the rate of platelet aggregation and the use of DHEA or DHEA-sulfate (DHEA-S) to reduce the production of thromboxane, respectively.

Nestler et al. (30) shows that administration of DHEA was able in human patients to reduce body fat mass, increase muscle mass, lower LDL cholesterol levels without affecting HDL cholesterol levels, lower serum apolipoprotein B levels, and not affect tissue sensitivity to insulin. Kent (31) reported DHEA to be a "miracle drug" which may prevent obesity, aging, diabetes mellitus and heart disease. DHEA was widely prescribed as a drug treatment for many years. However, the Food and Drug Administration recently restricted its use. DHEA is readily

interconvertible with its sulfate ester DHEA-S through the action of intracellular sulfatases and sulfotransferases.

Daynes et al. (32) shows that administration of certain DHEA derivatives are useful for the reducing or preventing progressive tissue necrosis, reperfusion injury, bacterial translocation and adult respiratory distress syndrome. Daynes et al. (33) shows that the administration of DHEAS and other DHEA derivatives are also suitable for these uses. Finally, Araneo et al. (34) shows that DHEA derivatives are useful for reducing or preventing pulmonary hypertension. Despite the myriad of biological activities reported for DHEA derivatives, DHEA derivatives have not been reported to have any affect on reducing CNS impairment.

SUMMARY OF THE INVENTION

The present invention is related to a method for reducing central nervous system (CNS) impairment, such as results from an ischemic event caused by a stroke or trauma to the central nervous system. In accordance with the present invention, CNS impairment is reduced by administering a dehydroepiandrosterone (DHEA) congener as soon as possible after the ischemic event.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 illustrates the experimental design for the central nervous system ischemia in the rabbit.

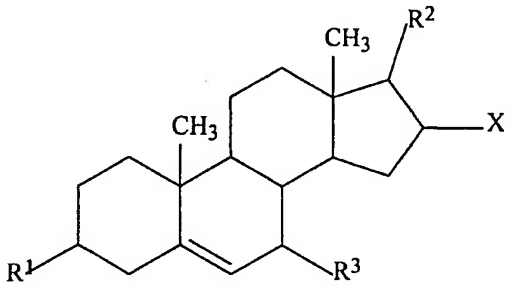
Figure 2 shows a graphic representation of the mean time required to produce paraplegia in 50% of the rabbits. A significant difference between high dose vs. low dose DHEA and between high dose vs. vehicle is seen in this study, with a $p<0.01$.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is related to a method for reducing central nervous system (CNS) impairment, such as results from an ischemic event caused by a stroke or trauma to the central nervous system. In accordance with the present invention, CNS impairment is reduced by administering a dehydroepiandrosterone (DHEA) congener as soon as possible after the ischemic event. As used herein, CNS impairment is intended to mean any impairment or damage to the CNS, including impairment and any neuronal damage. Thus, the use of a DHEA congener in

accordance with the present invention provides for neuroprotection for the CNS as a consequence of CNS ischemia or trauma.

Examples of a DHEA derivative include, but are not limited to, compounds having the general formula I



(I)

wherein

X is H or halogen;

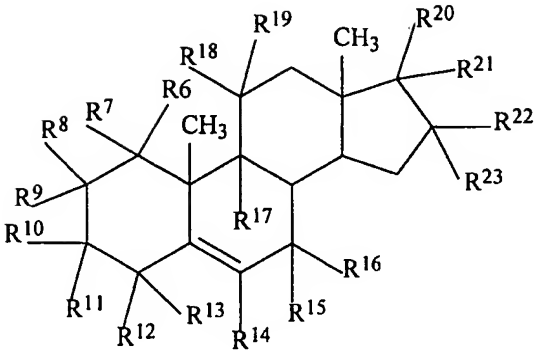
R^1 is =O, -OH, -SH, H, halogen, pharmaceutically acceptable ester, pharmaceutically acceptable thioester, pharmaceutically acceptable ether or pharmaceutically acceptable thioether;

R^2 and R^3 are independently =O, -OH, -SH, H, halogen, pharmaceutically acceptable ester, pharmaceutically acceptable thioester, pharmaceutically acceptable ether, pharmaceutically acceptable thioether, pharmaceutically acceptable inorganic esters, pharmaceutically acceptable monosaccharide, disaccharide or oligosaccharide, spirooxirane, spirothirane, $-OSO_2R^4$ or $-OPOR^4R^5$;

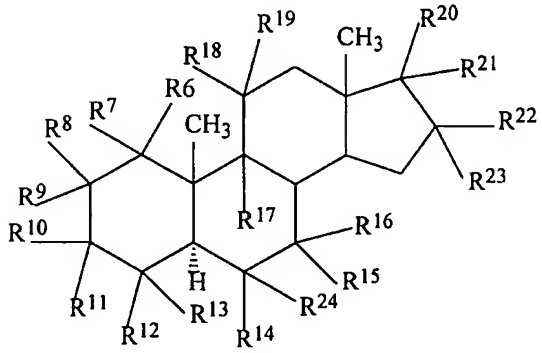
R^4 and R^5 are independently -OH, pharmaceutically acceptable esters or pharmaceutically acceptable ethers; and

pharmaceutically acceptable salts.

Further examples of a DHEA derivative, include but are not limited to, compounds having the general formulas II and III and their pharmaceutically acceptable salts



(II)



(III)

wherein

R^6, R^7, R^8, R^9, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19} and R^{24} are independently H, -OH, halogen, C_{1-10} alkyl or C_{1-10} alkoxy;

R^{10} is H, -0H, halogen, C_{1-10} alkyl, or C_{1-10} alkoxy;

R^{20} is (1) H, halogen, C_{1-10} alkyl or C_{1-10} alkoxy when R^{21} is -C(O)OR^{25} or

(2) H, halogen, OH or C_{1-10} alkyl when R^{21} is H, halogen, OH or C_{1-10} alkyl or

(3) H, halogen, C_{1-10} alkyl, C_{1-10} alkenyl, C_{1-10} alkynyl, formyl, C_{1-10} alkanoyl or epoxy when R^{21} is OH; or

R^{20} and R^{21} taken together are =O;

R^{22} and R^{23} are independently (1) H, -OH, halogen, C_{1-10} alkyl or C_{1-10} alkoxy when R^{21} is H, OH, halogen, C_{1-10} alkyl or -C(O)OR^{25} or

(2) H, $(C_{1-10}$ alkyl$)_n$amino, $(C_{1-10}$ alkyl$)_n$amino-C_{1-10} alkyl, C_{1-10} alkoxy, hydroxy-C_{1-10} alkyl, C_{1-10} alkoxy-C_{1-10} alkyl, $(\text{halogen})_m$-C_{1-10} alkyl,

C_{1-10} alkanoyl, formyl, C_{1-10} carbalkoxy or C_{1-10} alkanoyloxy when R^{20} and R^{21} taken together are =O; or

R^{22} and R^{23} taken together are =O or taken together with the carbon to which they are attached form a 3-6 member ring containing 0 or 1 oxygen atom; or

R^{20} and R^{22} taken together with the carbons to which they are attached form an epoxide ring;

R^{25} is H, $(halogen)_m$-C_{1-10} alkyl or C_{1-10} alkyl;

n is 0, 1 or 2;

m is 1, 2 or 3; and

physiologically acceptable salts thereof,

with the provisos that (a) R^{10} is not H, halogen, or C_{1-10} alkoxy when R^6, R^7, R^8, R^9, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{17}, R^{18}, R^{19} and R^{22} are H and R^{16} is H, halogen, OH or C_{1-10} alkoxy and R^{23} is H or halogen and R^{20} and R^{21} taken together are =O; and

(b) R^{10} is not H, halogen, or C_{1-10} alkoxy when R^6, R^7, R^8, R^9, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{17}, R^{18}, R^{19} and R^{22} are H and R^{16} is H, halogen, OH or C_{1-10} alkoxy and R^{23} is H or halogen and R^{20} is H and R^{21} is H, OH or halogen.

The compounds represented by the general formula I exist in many stereoisomers and the formula is intended to encompass the various stereoisomers. Examples of suitable DHEA congeners of Formula I include compounds in which:

(1) R^2 is =O, R^3 and X are each H and R^1 is =O, -OH, pharmaceutically acceptable esters thereof, pharmaceutically acceptable ethers thereof or pharmaceutically acceptable salts;

(2) R^2 is =O, R^3 is H, X is halogen and R^1 is =O, -OH, pharmaceutically acceptable esters thereof, pharmaceutically acceptable ethers thereof or pharmaceutically acceptable salts;

(3) R^2 is =O, R^3 and X are each H and R^1 is -SH, pharmaceutically acceptable thioesters thereof, pharmaceutically acceptable thioethers thereof or pharmaceutically acceptable salts;

(4) R^2 is =O, R^3 is H, X is halogen and R^1 is -SH, pharmaceutically acceptable thioesters thereof, pharmaceutically acceptable thioethers thereof or pharmaceutically acceptable salts;

(5) R^2 is =O, X is H and R^1 and R^3 are independently =O, -OH, pharmaceutically acceptable esters thereof, pharmaceutically acceptable ethers thereof or pharmaceutically acceptable salts;

(6) R^2 is =O, X is halogen and R^1 and R^3 are independently =O, -OH, pharmaceutically acceptable esters thereof, pharmaceutically acceptable ethers thereof or pharmaceutically acceptable salts;

(7) R^2 is =O, X is H and R^1 and R^3 are independently -SH, pharmaceutically acceptable thioesters thereof, pharmaceutically acceptable thioethers thereof or pharmaceutically acceptable salts;

(8) R^2 is =O, X is halogen and R^1 and R^3 are independently -SH, pharmaceutically acceptable thioesters thereof, pharmaceutically acceptable thioethers thereof or pharmaceutically acceptable salts;

(9) R^2 is -OH, R^3 and X are each H and R^1 is =O, -OH, pharmaceutically acceptable esters thereof, pharmaceutically acceptable ethers thereof or pharmaceutically acceptable salts;

(10) R^2 is -OH, R^3 is H, X is halogen and R^1 is =O, -OH, pharmaceutically acceptable esters thereof, pharmaceutically acceptable ethers thereof or pharmaceutically acceptable salts;

(11) R^2 is -OH, R^3 and X are each H and R^1 is -SH, pharmaceutically acceptable thioesters thereof, pharmaceutically acceptable thioethers thereof or pharmaceutically acceptable salts;

(12) R^2 is -OH, R^3 is H, X is halogen and R^1 is -SH, pharmaceutically acceptable thioesters thereof, pharmaceutically acceptable thioethers thereof or pharmaceutically acceptable salts;

(13) R^2 is -OH, X is H and R^1 and R^3 are independently =O, -OH, pharmaceutically acceptable esters thereof, pharmaceutically acceptable ethers thereof or pharmaceutically acceptable salts;

(14) R^2 is -OH, X is halogen and R^1 and R^3 are independently =O, -OH, pharmaceutically acceptable esters thereof, pharmaceutically acceptable ethers thereof or pharmaceutically acceptable salts;

(15) R^2 is -OH, X is H and R^1 and R^3 are independently -SH, pharmaceutically acceptable thioesters thereof, pharmaceutically acceptable thioethers thereof or pharmaceutically acceptable salts;

(16) R^2 is -OH, X is halogen and R^1 and R^3 are independently -SH, pharmaceutically acceptable thioesters thereof, pharmaceutically acceptable thioethers thereof or pharmaceutically acceptable salts;

(17) R^2 is -SH, R^3 and X are each H and R^1 is =O, -OH, pharmaceutically acceptable esters thereof, pharmaceutically acceptable ethers thereof or pharmaceutically acceptable salts;

(18) R^2 is -SH, R^3 is H, X is halogen and R^1 is =O, -OH, pharmaceutically acceptable esters thereof, pharmaceutically acceptable ethers thereof or pharmaceutically acceptable salts;

(19) R^2 is -SH, R^3 and X are each H and R^1 is -SH, pharmaceutically acceptable thioesters thereof, pharmaceutically acceptable thioethers thereof or pharmaceutically acceptable salts;

(20) R^2 is -SH, R^3 is H, X is halogen and R^1 is -SH, pharmaceutically acceptable thioesters thereof, pharmaceutically acceptable thioethers thereof or pharmaceutically acceptable salts;

(21) R^2 is -SH, X is H and R^1 and R^3 are independently =O, -OH, pharmaceutically acceptable esters thereof, pharmaceutically acceptable ethers thereof or pharmaceutically acceptable salts;

(22) R^2 is -SH, X is halogen and R^1 and R^3 are independently =O, -OH, pharmaceutically acceptable esters thereof, pharmaceutically acceptable ethers thereof or pharmaceutically acceptable salts;

(23) R^2 is -SH, X is H and R^1 and R^3 are independently -SH, pharmaceutically acceptable thioesters thereof, pharmaceutically acceptable thioethers thereof or pharmaceutically acceptable salts;

(24) R^2 is -SH, X is halogen and R^1 and R^3 are independently -SH, pharmaceutically acceptable thioesters thereof, pharmaceutically acceptable thioethers thereof or pharmaceutically acceptable salts;

(25) X is H and R^1 is =O, -OH, pharmaceutically acceptable esters thereof, pharmaceutically acceptable ethers thereof or pharmaceutically acceptable salts, R^2 and R^3 are independently =O, -OH, a sugar residue, pharmaceutically acceptable esters thereof, pharmaceutically acceptable ethers thereof or pharmaceutically acceptable salts, wherein at least one of R^2 and R^3 is a sugar residue;

(26) X is halogen and R^1 is =O, -OH, pharmaceutically acceptable esters thereof, pharmaceutically acceptable ethers thereof or pharmaceutically acceptable salts, R^2 and R^3 are independently =O, -OH, a sugar residue, pharmaceutically acceptable esters thereof,

pharmaceutically acceptable ethers thereof or pharmaceutically acceptable salts, wherein at least one of R^2 and R^3 is a sugar residue;

(27) X is H, R^1 is =O or -OH, and R^2 and R^3 are independently =O, -OH, pharmaceutically acceptable inorganic esters thereof or pharmaceutically acceptable salts, wherein at least one of R^2 and R^3 is an inorganic ester;

(28) X is halogen R^1 is =O or -OH, and R^2 and R^3 are independently =O, -OH, pharmaceutically acceptable inorganic esters thereof or pharmaceutically acceptable salts, wherein at least one of R^2 and R^3 is an inorganic ester.

Pharmaceutically acceptable esters or thioesters include, but are not limited to, esters or thioesters of the formula -OOCR or -SOCR, wherein R is a pharmaceutically acceptable alkyl, alkenyl, aryl, alkylaryl, arylalkyl, sphingosine or substituted sphingolipid groups, such as propionate, enanthate, cypionate, succinate, decanoate and phenylpropionate esters.

Pharmaceutically acceptable ethers or thioethers include, but are not limited to, ethers or thioethers of the formula -OR or -SR, wherein R is as defined above or enol, or -OR is an unsubstituted or substituted spirooxirane or -SR is a spirothiane.

Suitable sugar residues include, but are not limited to monosaccharides, disaccharides and oligosaccharides, such as a glucuronate.

Pharmaceutically acceptable inorganic esters include, but are not limited to, inorganic esters of the formula $-OSO_2R^4$ or $-OPOR^4R^5$, wherein R^4 and R^5 are independently -OH, pharmaceutically acceptable esters, pharmaceutically acceptable ethers or pharmaceutically acceptable salts.

Compounds of general formulas II and III are synthesized as described in U.S. Patent Nos. 4,898,694; 5,001,119; 5,028,631; and 5,175,154, incorporated herein by reference. The compounds represented by the general formulas II and III exist in many stereoisomers and these formulas are intended to encompass the various stereoisomers. Examples of representative compounds which fall within the scope of general formulas II and III include the following:

5α-androstan-17-one;

16α-fluoro-5α-androstan-17-one;

3β-methyl-5α-androsten-17-one;

16α-fluoro-5α-androstan-17-one;

17β-bromo-5-androsten-16-one;

17β-fluoro-3β-methyl-5-androsten-16-one;

17α-fluoro-5α-androstan-16-one;

3β-hydroxy-5-androsten-17-one;

17α-methyl-5α-androstan-16-one;

16α-methyl-5-androsten-17-one;

3β,16α-dimethyl-5-androsten-17-one;

3β,17α-dimethyl-5-androsten-16-one;

16α-hydroxy-5-androsten-17-one;

16α-fluoro-16β-methyl-5-androsten-17-one;

16α-methyl-5α-androstan-17-one;

16-dimethylaminomethyl-5α-androstan-17-one;

16β-methoxy-5-androsten-17-one;

16α-fluoromethyl-5-androsten-17-one;

16-methylene-5-androsten-17-one;

16-cyclopropyl-5α-androstan-17-one;

16-cyclobutyl-5-androsten-17-one;

16-hydroxymethylene-5-androsten-17-one;

3α-bromo-16α-methoxy-5-androsten-17-one;

16-oxymethylene-5-androsten-17-one;

3β-methyl-16ξ-trifluoromethyl-5α-androstan-17-one;

16-carbomethoxy-5-androsten-17-one;

3β-methyl-16β-methoxy-5α-androstan-17-one;

3β-hydroxy-16α-dimethylamino-5-androsten-17-one;

17α-methyl-5-androsten-17β-ol;

17α-ethynyl-5α-androstan-17β-ol;

17β-formyl-5α-androstan-17β-ol;

20,21-epoxy-5α-pregnan-17α-ol;

3β-hydroxy-20,21-epoxy-5α-pregnan-17α-ol;

16α-fluoro-17α-ethenyl-5-androsten-17β-ol;

16α-hydroxy-5-androsten-17α-ol;

16α-methyl-5α-androstan-17α-ol;

16α-methyl-16β-fluoro-5α-androstan-17α-ol;

16α-methyl-16β-fluoro-3-hydroxy-5-androsten-17α-ol;

3β,16β-dimethyl-5-androsten-17β-ol;

3β,16,16-trimethyl-5-androsten-17β-ol;

3β,16,16-trimethyl-5-androsten-17-one;

3β-hydroxy-4α-methyl-5-androsten-17α-ol;

3β-hydroxy-4α-methyl-5-androsten-17-one;

3α-hydroxy-1α-methyl-5-androsten-17-one;

3α-ethoxy-5α-androstan-17β-ol;

5α-pregnan-20-one;

3β-methyl-5α-pregnan-20-one;

16α-methyl-5-pregnen-20-one;

16α-methyl-3β-hydroxy-5-pregnen-20-one;

17α-fluoro-5-pregnen-20-one;

21-fluoro-5α-pregnan-20-one;

17α-methyl-5-pregnen-20-one;

20-acetoxy-cis-17(20)-5α-pregnene;

3α-methyl-16,17-epoxy-5-pregnen-20-one.

The effectiveness of the DHEA congeners in reducing CNS impairment has been examined in an animal system which is widely used as a model for human stroke. The animal system is a rabbit spinal cord ischemia model (35). This model is highly reproducible and the neurological deficits that evolve over the 24 hours following the ischemic event are remarkably similar to human cerebrovascular insufficiency syndromes in humans. The model is able to demonstrate differences between brief ischemia, intermediate ischemic periods and prolonged ischemia. Brief ischemia produces completely reversible neurological deficits. Intermediate ischemia produces transiently reversible deficits that later progress without further manipulation. Prolonged ischemia produces irreversible lesions in all animals. These patterns are similar to those seen in human transient ischemic attacks (TIAs), stroke-in-evolution (SIE) and complete infarction. This model system is particularly suited for the study of SIE. The administration of a DHEA congener, currently preferred to be DHEA, in this model demonstrates that CNS impairment is reduced by this treatment. Thus, this model demonstrates the neuroprotective

ability of DHEA congeners for the treatment of CNS ischemia or trauma, such as stroke, head injuries or spinal cord injuries.

Pharmaceutical compositions containing a compound of the present invention as the active ingredient can be prepared according to conventional pharmaceutical compounding techniques (36). Typically, a therapeutically effective amount of the active ingredient will be admixed with a pharmaceutically acceptable carrier. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral, preferably parenteral, such as intravenous, intrathecal and epidural. It is preferred to administer the active agent by intravenous administration or by a combination of intrathecal or epidural administration and intravenous infusion. The compositions may further contain antioxidizing agents, stabilizing agents, preservatives and the like.

For oral administration, the compounds can be formulated into solid or liquid preparations such as capsules, pills, tablets, lozenges, melts, powders, suspensions or emulsions. In preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, suspending agents, and the like in the case of oral liquid preparations (such as, for example, suspensions, elixirs and solutions); or carriers such as starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like in the case of oral solid preparations (such as, for example, powders, capsules and tablets). Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be sugar-coated or enteric-coated by standard techniques. The active agent can be encapsulated to make it stable to passage through the gastrointestinal tract while at the same time allowing for passage across the blood brain barrier. See for example, WO 96/11698, incorporated herein by reference.

For parenteral administration, the compound or a complex of the compound and a cyclodextrin may be dissolved in a pharmaceutical carrier and administered as either a solution or a suspension. It is preferred to use a complex of the active agent and a cyclodextrin, preferably 2-hydroxypropyl β-cyclodextrin, such as prepared in accordance with U.S. Patent No. 4,727,064 and/or European Patent No. 0 149 197, each incorporated herein by reference. The use of the compound as part of a cyclodextrin complex allows for the preparation of parenteral

solutions with high concentration of active agent. Illustrative of suitable carriers are water, saline, dextrose solutions, fructose solutions, ethanol, or oils of animal, vegetative or synthetic origin. The carrier may also contain other ingredients, for example, preservatives, suspending agents, solubilizing agents, buffers and the like. When the compounds are being administered intrathecally, they or their cyclodextrin complexes may also be dissolved in cerebrospinal fluid.

The dose of the DHEA congener is based on well known pharmaceutically acceptable principles to deliver a DHEA equivalent dose of, e.g., from about 1.0 mg/kg to about 75 mg/kg, preferably from about 1.0 mg/kg to about 50 mg/kg, more preferably from about 5.0 mg/kg to about 50 mg/kg and most preferably from about 5.0 mg/kg to about 30 mg/kg. If the DHEA congener is administered intravenously or by infusion, a DHEA equivalent dose of, e.g., from about 1.0 mg/kg/hr to about 75 mg/kg/hr, preferably from about 1.0 mg/kg/hr to about 50 mg/kg/hr, more preferably from about 1.0 mg/kg/hr to about 30 mg/kg/hr, most preferably from about 2.5 mg/kg/hr to about 25 mg/kg/hr, is administered. If the DHEA congener is administered initially as a bolus of the DHEA congener, it is preferred to administer a DHEA equivalent dose of, e.g., from about 1.0 mg/kg to about 75 mg/kg, preferably from about 5.0 mg/kg to about 50 mg/kg, more preferably from about 5.0 mg/kg to about 30 mg/kg and most preferably from about 10.0 mg/kg to about 30 mg/kg. For unprotected compounds, i.e., those which can be sulfated by human sulfotransferases or sulfatases, it is preferred to administer an excess dose to insure that sufficient active agent is administered, especially if sulfatases are not active at the site of administration.

In accordance with conventional treatment of CNS ischemia or trauma such as stroke, head injuries and spinal chord injuries, it is important that the DHEA congener be administered as soon after the CNS ischemia or trauma as possible. It is preferred that the DHEA congener be administered within 8 hours, preferably within 4 hours, more preferably within 2 hours and most preferably within 1 hour following the CNS ischemia or trauma. The DHEA congener is administered to the patient for 1-6 hours, preferably 2-5 hours, more preferably 3-4 hours and most preferably 4 hours, following the start of administration of the DHEA congener. The DHEA congener can be administered intravenously by infusion in the dose described above, or it can be administered as a first administration of a bolus of the active agent in the dose described above and a second administration of the active agent by intravenous infusion in the dose described above. The bolus of the active agent can be administered intravenously, intrathecally or epineurally. It is

currently preferred to administer the active agent as the combination of an intravenous bolus administration and an intravenous infusion administration.

The present invention is described by reference to the following Examples, which are offered by way of illustration and are not intended to limit the invention in any manner. Standard techniques well known in the art or the techniques specifically described below were utilized.

EXAMPLE 1

Effect of DHEA in the Rabbit Stroke Model

Young adult New Zealand male albino rabbits weighting 2-3 kilograms were maintained in individual cages and allowed to food and water ad-lib for three to five days before surgery. They were anesthetized with ketamine, 20 mg/kg, and open-drop ether. Through a midline abdominal incision, the aorta was exposed at the level of the renal arteries. A PE10 polyethylene catheter was placed around the aorta just distal to the left infrarenal artery. The ends of the catheter were threaded through a 7-mm diameter plastic button and then a 3.18-mm internal diameter polyvinyl chloride tube to form a snare ligature. The incision was closed around the tubing so the free ends were accessible externally. The rabbits were allowed to recover from the anesthesia for two to four hours. At this time, it was possible to establish that the rabbits' sensations and motor activities were normal. We then occluded the aorta of each animal by pulling on the polyethylene catheter. Adequacy of this method of vascular occlusion was validated in previous experiments. After a precise interval, release of the catheter allowed restoration of flow through the infrarenal artery and into the central nervous system.

In this study, rabbits were randomized to treatment groups and to predetermined times of vascular occlusion. For each treatment arm, a minimum of two rabbits were occluded for a predetermined interval of 15 to 60 minutes of occlusion. Vehicle subjects consisted of 18 evaluable rabbits given an equivalent volume of vehicle substance in a bolus and 60-minute infusion starting five minutes after ischemia. Low-dose DHEA (as cyclodextrin complex) was administered as a bolus dose of 5 mg/kg and an infusion of 2.5 mg/kg/1 hour, starting five minutes after ischemia. High-dose DHEA (as cyclodextrin complex) was administered as a bolus of 15 mg/kg, followed by an infusion of 7.5 mg/kg/1 hour. Figure 1 graphically illustrates the design of this experiment.

The animals were observed continuously while the aorta was occluded and for 30 minutes following release of the ligature. They were then examined at 30 minute intervals for the next three hours and twice daily for four days. The presence of neurologic impairment was ascertained at 24 hours by a blinded observer. Rabbits were normal if they ambulated normally, responded normally to noxious stimuli, and had normal bowel and bladder function. Rabbits were abnormal if they showed any form of paraplegia, including the inability to hop normally, to respond to pinching of the hind limbs or complete paralysis. Bowel and bladder function was variable. Animals showing any degree of impairment of these clinical factors were scored as abnormal.

To evaluate the relationship between the duration of aortic occlusion and the fraction of animals showing development of neurologic dysfunction quantitatively, logistic curves were fitted to the quantal dose-response data by use of an iterative technique based on a Taylor series expansion. The differences in the curves were tested by a conservative use of group t tests ($p<0.01$).

The rabbits became paraplegic immediately when the snare ligature was pulled tight. A few maintained sensory or motor functions for several seconds after initiation of occlusion, but all animals became completely paraplegic within one minute. When the ligature was released, one of four patterns are typically observed. One is the immediate or gradual return to normal over the 24 hours, another is incomplete recovery with partial paraplegia that remained unchanged for 24 hours, another is the immediate return to normal and then progressing paraplegia over the next 24 hours, and finally persistence of complete paraplegia for the 24-hour period. The design of the experiment was such that no deficits reversed over the total four-day observation period. The neurologic impairment resulting from each progressive interval of ischemia is given in the tables below.

TABLE I

Neurologic Scores on Rabbits in Vehicle-Treated Group

Interval of CNS Ischemia	*Normal*	*Abnormal*
15	1	0
16	1	0
17	2	0
18	1	0
20	0	1
21	1	0
23	0	1
24	0	1
32	0	1
33	1	0
36	0	2
37	0	1
46	0	1
55	0	2
60	0	1

TABLE II

Neurologic Scores on Rabbits in Low-Dose PB007-Treated Group

Interval of CNS Ischemia	*Normal*	*Abnormal*
15	1	0
18	2	0
25	0	1
26	1	1
27	0	1
28	0	1
29	0	1
30	0	1
33	0	1
34	0	1
35	0	1
40	0	1
41	1	0
46	0	1
50	0	1

TABLE III

Neurologic Scores on Rabbits in High-Dose PB007-Treated Group

Interval of CNS Ischemia	*Normal*	*Abnormal*
18	1	0
21	1	0
22	2	0
27	1	0
29	1	0
30	1	0
31	0	1
32	1	0
33	0	1
34	1	0
35	1	0
40	0	1
42	0	1
48	0	1

Figure 2 shows a graphic representation of the mean time required to produce paraplegia in 50% of the rabbits. A significant difference between high dose vs. low dose PB007 and between high dose vs. vehicle was observed in this study, with a $p<0.01$. Thus, this experiment demonstrates that the administration of DHEA has a beneficial outcome on the pathogenesis of stroke-in-evolution and is able to reduce CNS impairment as a consequence of CNS ischemia or trauma.

It will be appreciated that the methods and compositions of the instant invention can be incorporated in the form of a variety of embodiments, only a few of which are disclosed herein. It will be apparent to the artisan that other embodiments exist and do not depart from the spirit of the invention. Thus, the described embodiments are illustrative and should not be construed as restrictive.

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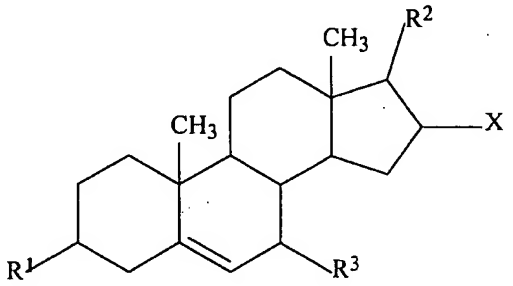
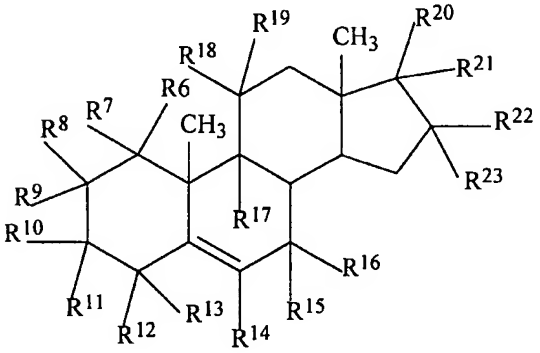
WHAT IS CLAIMED IS:

1. Use of a dehydroepiandrosterone (DHEA) congener of Formula I, Formula II or Formula III for preparing a pharmaceutical composition for reducing central nervous system impairment as a consequence of central nervous system ischemia or trauma:



(I)



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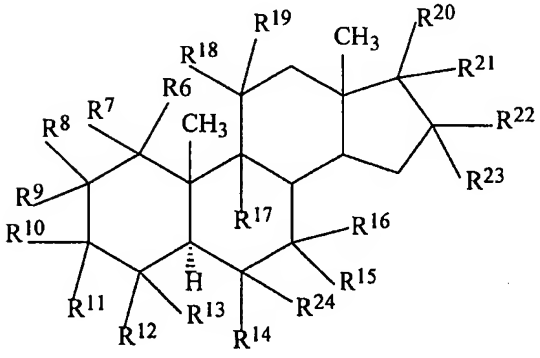


(III)

wherein

X is H or halogen;

R^1 is =O, -OH, -SH, H, halogen, pharmaceutically acceptable ester, pharmaceutically acceptable thioester, pharmaceutically acceptable ether or pharmaceutically acceptable thioether;

R^2 and R^3 are independently =O, -OH, -SH, H, halogen, pharmaceutically acceptable ester, pharmaceutically acceptable thioester, pharmaceutically acceptable ether, pharmaceutically acceptable thioether, pharmaceutically acceptable inorganic esters, pharmaceutically acceptable monosaccharide, disaccharide or oligosaccharide, spirooxirane, spirothirane, $-OSO_2R^5$ or $-OPOR^5R^6$;

R^5 and R^6 are independently -OH, pharmaceutically acceptable esters or pharmaceutically acceptable ethers;

R^6, R^7, R^8, R^9, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19} and R^{24} are independently H, -OH, halogen, C_{1-10} alkyl or C_{1-10} alkoxy;

R^{10} is H, -0H, halogen, C_{1-10} alkyl, or C_{1-10} alkoxy;

R^{20} is (1) H, halogen, C_{1-10} alkyl or C_{1-10} alkoxy when R^{21} is $-C(O)OR^{25}$ or

(2) H, halogen, OH or C_{1-10} alkyl when R^{21} is H, halogen, OH or C_{1-10} alkyl

or

(3) H, halogen, C_{1-10} alkyl, C_{1-10} alkenyl, C_{1-10} alkynyl, formyl, C_{1-10} alkanoyl or epoxy when R^{21} is OH; or

R^{20} and R^{21} taken together are =O;

R^{22} and R^{23} are independently (1) H, -OH, halogen, C_{1-10} alkyl or C_{1-10} alkoxy when R^{21} is H, OH, halogen, C_{1-10} alkyl or $-C(O)OR^{25}$ or

(2) H, $(C_{1-10}$ alkyl$)_n$amino, $(C_{1-10}$ alkyl$)_n$amino-C_{1-10} alkyl, C_{1-10} alkoxy, hydroxy-C_{1-10} alkyl, C_{1-10} alkoxy-C_{1-10} alkyl, $(\text{halogen})_m$-C_{1-10} alkyl, C_{1-10} alkanoyl, formyl, C_{1-10} carbalkoxy or C_{1-10} alkanoyloxy when R^{20} and R^{21} taken together are =O; or

R^{22} and R^{23} taken together are =O or taken together with the carbon to which they are attached form a 3-6 member ring containing 0 or 1 oxygen atom; or

R^{20} and R^{22} taken together with the carbons to which they are attached form an epoxide ring;

R^{25} is H, $(\text{halogen})_m$-C_{1-10} alkyl or C_{1-10} alkyl;

n is 0, 1 or 2;

m is 1, 2 or 3; and

pharmaceutically acceptable salts thereof,

with the provisos that (a) R^{10} is not H, halogen, or C_{1-10} alkoxy when R^6, R^7, R^8, R^9, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{17}, R^{18}, R^{19} and R^{22} are H and R^{16} is H, halogen, OH or C_{1-10} alkoxy and R^{23} is H or halogen and R^{20} and R^{21} taken together are =O; and

(b) R^{10} is not H, halogen, or C_{1-10} alkoxy when R^6, R^7, R^8, R^9, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{17}, R^{18}, R^{19} and R^{22} are H and R^{16} is H, halogen, OH or C_{1-10} alkoxy and R^{23} is H or halogen and R^{20} is H and R^{21} is H, OH or halogen.

2. The use of claim 1 wherein the DHEA congener is a compound of Formula I.

3. The use of claim 1 wherein the DHEA congener is a compound of Formula II.

4. The use of claim 1 wherein the DHEA congener is a compound of Formula III.

5. The use of claim 1 wherein the DHEA congener is DHEA.

6. The use of any one of claims 1-5 wherein an effective amount of the DHEA congener is from about 1.0 mg/kg to about 75 mg/kg.

7. The use of any one of claims 1-5 wherein the DHEA congener is administered intravenously.

8. The use of claim 7 wherein an effective amount of the DHEA congener is from about 1.0 mg/kg to about 50 mg/kg.

9. The use of claim 7 wherein an effective amount of the DHEA congener is from about 5.0 mg/kg to about 50 mg/kg.

10. The use of claim 7 wherein an effective amount of the DHEA congener is from about 5.0 mg/kg to about 30 mg/kg.

11. The use of any one of claims 1-5 wherein a bolus of the DHEA congener is administered followed by an intravenous infusion of the DHEA congener.

12. The use of claim 11 wherein the bolus of the DHEA congener is first administered intravenously.

13. The use of claim 11 wherein the bolus of the DHEA congener is administered intrathecal or epineural.

14. The use of claim 11 wherein an effective amount of the bolus of the DHEA congener is from about 1.0 mg/kg to about 75 mg/kg.

15. The use of claim 11 wherein an effective amount of the bolus of the DHEA congener is from about 5.0 mg/kg to about 50 mg/kg.

16. The use of claim 11 wherein an effective amount of the bolus of the DHEA congener is from about 5.0 mg/kg to about 30 mg/kg.

17. The use of claim 11 wherein an effective amount of the intravenous infusion of the DHEA congener is from about 1.0 mg/kg/hr to about 75 mg/kg/hr.

18. The use of claim 11 wherein an effective amount of the intravenous infusion of the DHEA congener is from about 1.0 mg/kg/hr to about 50 mg/kg/hr.

19. The use of claim 11 wherein an effective amount of the intravenous infusion of the DHEA congener is from about 1.0 mg/kg/hr to about 30 mg/kg/hr.

20. A method for reducing central nervous system impairment as a consequence of central nervous system ischemia or trauma which comprises administering to a patient having suffered said ischemia or trauma a therapeutically effective amount of a

dehydroepiandrosterone (DHEA) congener of Formula I, Formula II or Formula III as set forth in claim1.

21. The method of claim 20 wherein the DHEA congener is administered intravenously.

22. The method of claim 21 wherein an effective amount of the DHEA congener is from about 1.0 mg/kg to about 75 mg/kg.

23. The method of claim 20 wherein a bolus of a DHEA congener is first administered followed by an intravenous infusion of a DHEA congener.

24. The method of claim 23 wherein the bolus of the DHEA congener is administered intravenously.

25. The method of claim 23 wherein the bolus of the DHEA congener is administered intrathecal or epineural.

26. The method of claim 23 wherein the effective amount of the bolus administration of the DHEA congener is from about 1.0 mg/kg to about 75 mg/kg.

27. The method of claim 23 wherein the effective amount of the intravenous infusion of the DHEA congener is from about 1.0 mg/kg/hr to about 75 mg/kg/hr.

28. The method of claim 26 wherein the effective amount of the intravenous infusion of the DHEA congener is from about 1.0 mg/kg/hr to about 75 mg/kg/hr.

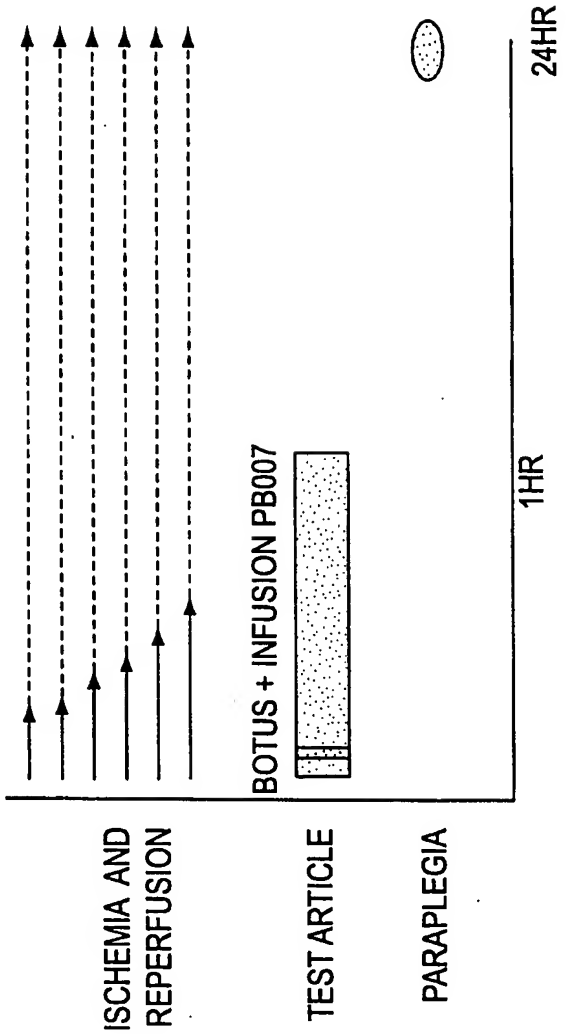
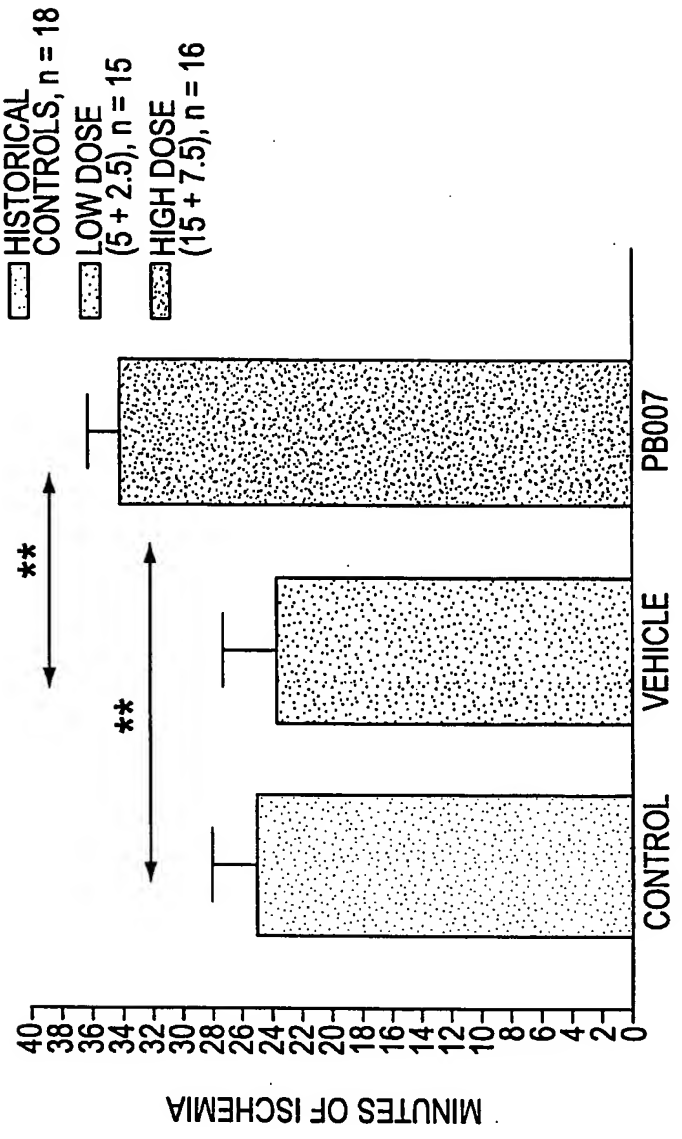

ISCHEMIA AND REPERFUSION
BOTUS + INFUSION PB007
TEST ARTICLE
PARAPLEGIA
1HR
24HR
TOTAL TIME (HOURS)

FIG. 1


HISTORICAL CONTROLS, n = 18
LOW DOSE (5 + 2.5), n = 15
HIGH DOSE (15 + 7.5), n = 16
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CONTROL
VEHICLE
PB007
TREATMENT
MINUTES OF ISCHEMIA
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FIG. 2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/07319

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :A61K 31/56, 31/705
US CL :514/178, 26
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/178, 26

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, 5,162,198 A (EICH et al.) 10 November 1992, see column 9, line 50 to column 10, line 13.	1-28
Y	US 5,532,230 A (DAYNES et al.) 02 July 1996, see column 8, line 3 to column 9, line 10, and column 11, lines 16-21.	1-28

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"B"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 07 MAY 1999	Date of mailing of the international search report 19MAY 1999
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer KATHLEEN KAHLER FONDA Telephone No. (703) [illegible]-1235

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/07319

B. FIELDS SEARCHED
Electronic data bases consulted (Name of data base and where practicable terms used):

Databases: APS, REGISTRY, HCAPLUS
search terms: inventor names, structures, ?androstero?, dhea, ?ischemi?, ?trauma?, infarct?, stroke#

IE 950377

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The Patents Office

ABSTRACT

Formulation techniques for the preparation of colloidal suspensions for therapeutic administration

Herein is described a specific combination pharmaceutical formulation method, hitherto unknown, for therapeutic use. These therapeutic formulations contain 17-Ketosteroid in combination with a polyadditive nonionic surfactants. These polyadditive nonionic surfactants are known as block polymers or "pluronics" (CTFA: poloxamers) they are polycondensates of ethylene oxide and propylene oxide. These formulations provide a means for drug delivery of a 17-ketosteroid in a colloidal suspension. Intravenously injected colloidal particle suspensions of these formulations become localised in tissues of the reticuloendothelial and lymphoid system in mammals. These colloidal suspensions may be administered in the form of eye drops. In addition the said formulation may also contain metoclopramide to enhance its therapeutic benefit. The said 17-ketosteroid may be in micronized form for the preparation of the colloidal suspension.